Armed Forces College of Medicine

AFCM

Hormone action and signal transduction

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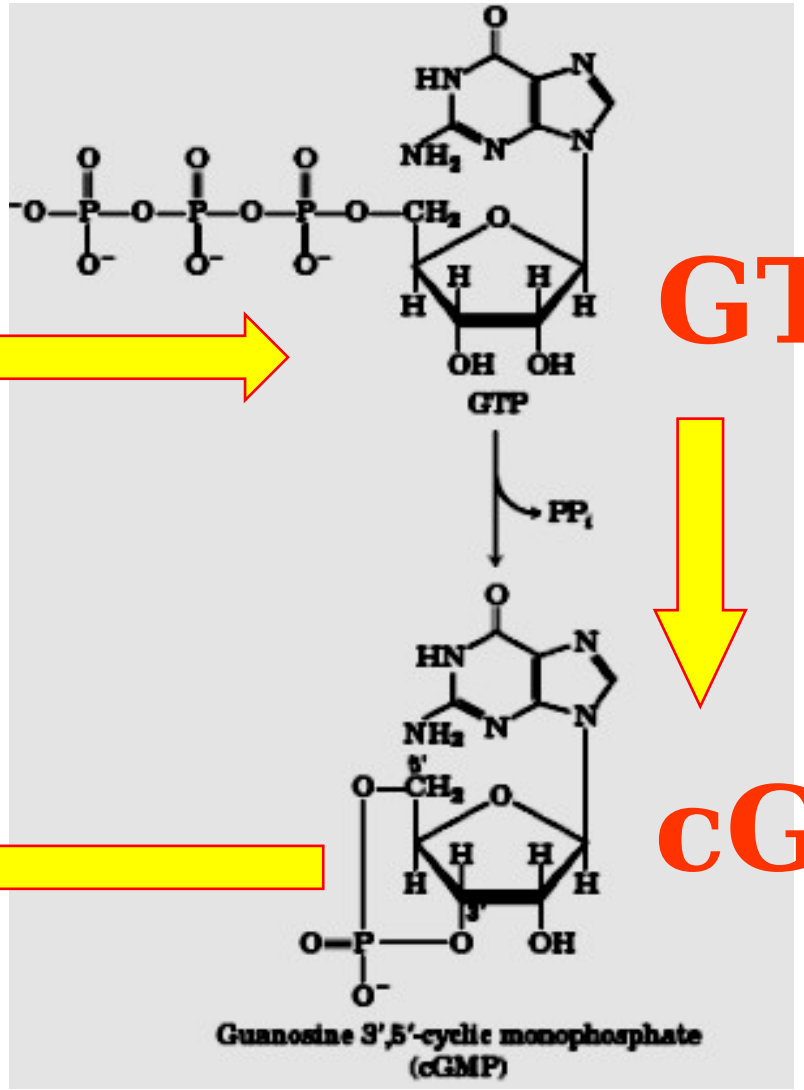
INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. **Explain mechanism of action of hormones using cGMP as second messenger.**
2. **Discuss mechanism of action of hormones acting on tyrosine kinases.**

3- cGMP as a second messenger

Guanylyl cyclase activity



GTP

cGMP

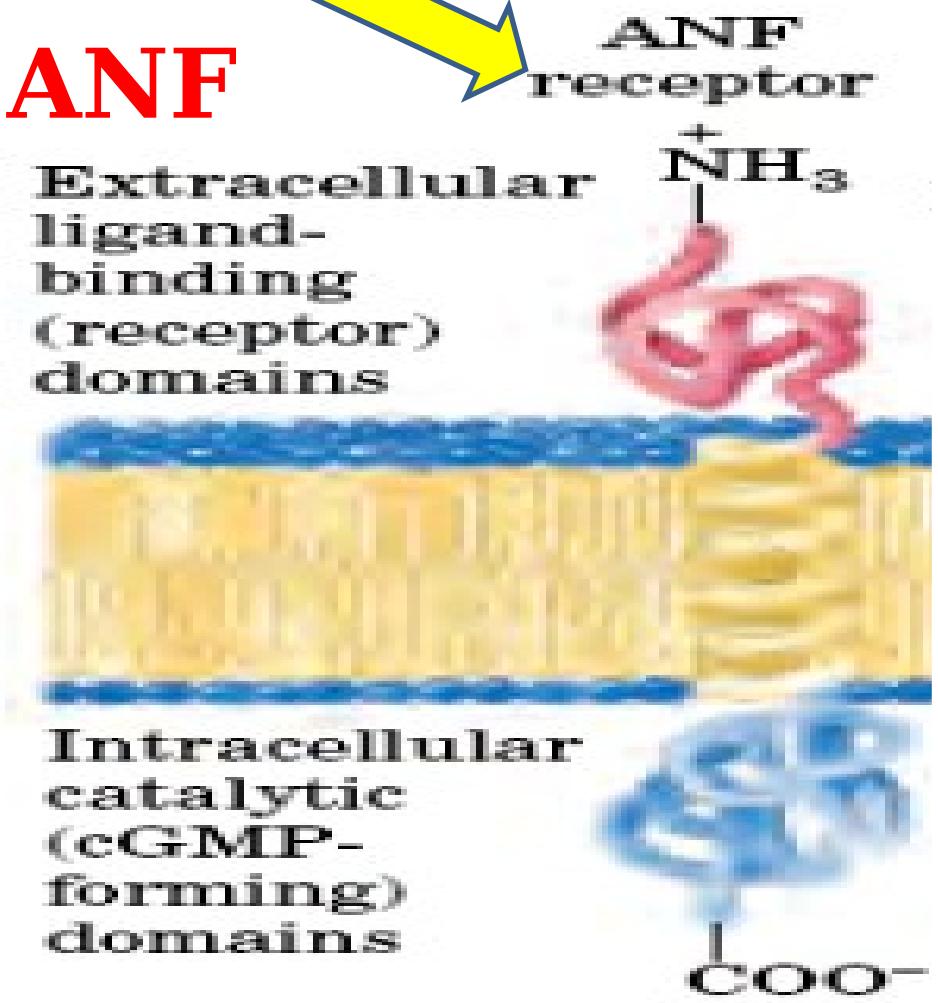
Activation of cGMP dependant protein kinase (PKG)

Factors that depend on cGMP as a second messenger:

- **Atrial natriuretic factor (ANF)**
- **Nitric Oxide (NO)**

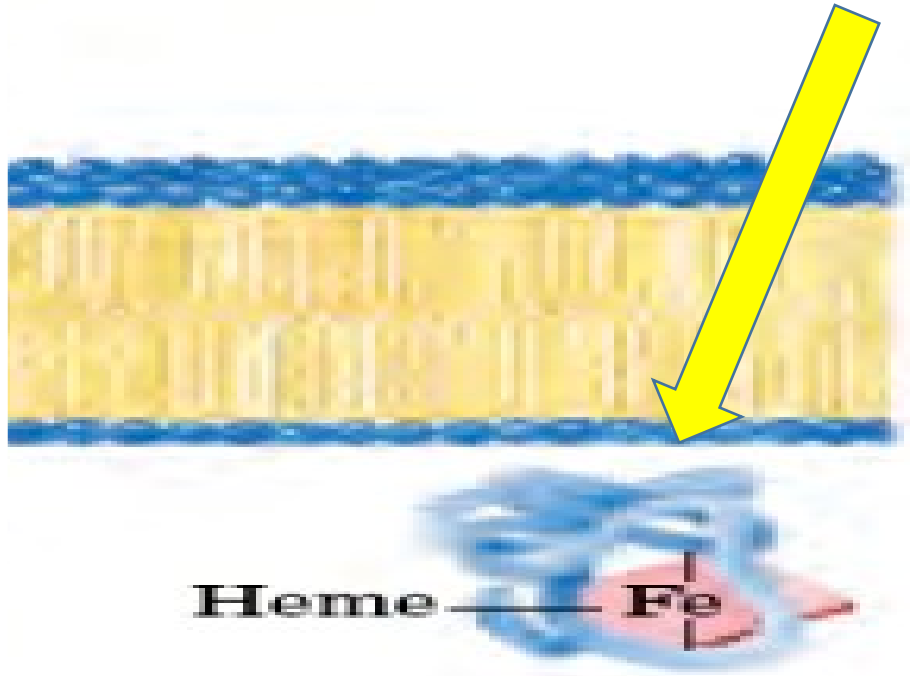
There are two types of Guanyl cyclase

ANF



Membrane-spanning guanylyl cyclases

Nitric Oxide



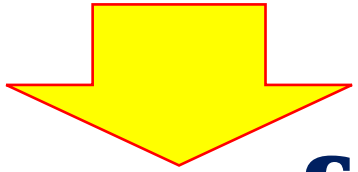
Soluble NO-activated guanylyl cyclase

Atrial Natruretic factor (ANF)

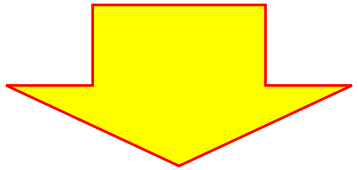
Effect of ANF

This peptide is produced in cardiac atrial tissues

It binds to and activates the membrane-bound form of guanylyl cyclase in the kidney



increase of cGMP



Natriuresis, diuresis thus decreasing blood volume

Nitric Oxide (NO)

Effect of NO

A series of nitrovasodilators including, *nitroglycerin* are used to treat *Angina*

Increase *cGMP* by activating the soluble form of guanylyl cyclase

Activates cGMP-dependent protein kinase (PKG),

Phosphorylates a number of smooth muscle proteins

Relaxation of smooth muscle and vasodilation

What secondary messenger is generated as a result of the action of nitrous oxide?

a) GTP

b) cyclic GMP

c) ATP

d) cyclic AMP

4- Second messenger is a Kinase

There are two types of receptors:

A- The receptor has an *intrinsic tyrosine Kinase* activity (as *Insulin* hormone *receptor*)

B- The receptor lacks tyrosine kinase activity but *activates cytosolic kinases* (as *Growth hormone* receptor)

A- Signal transduction through receptors with intrinsic tyrosine kinase activity

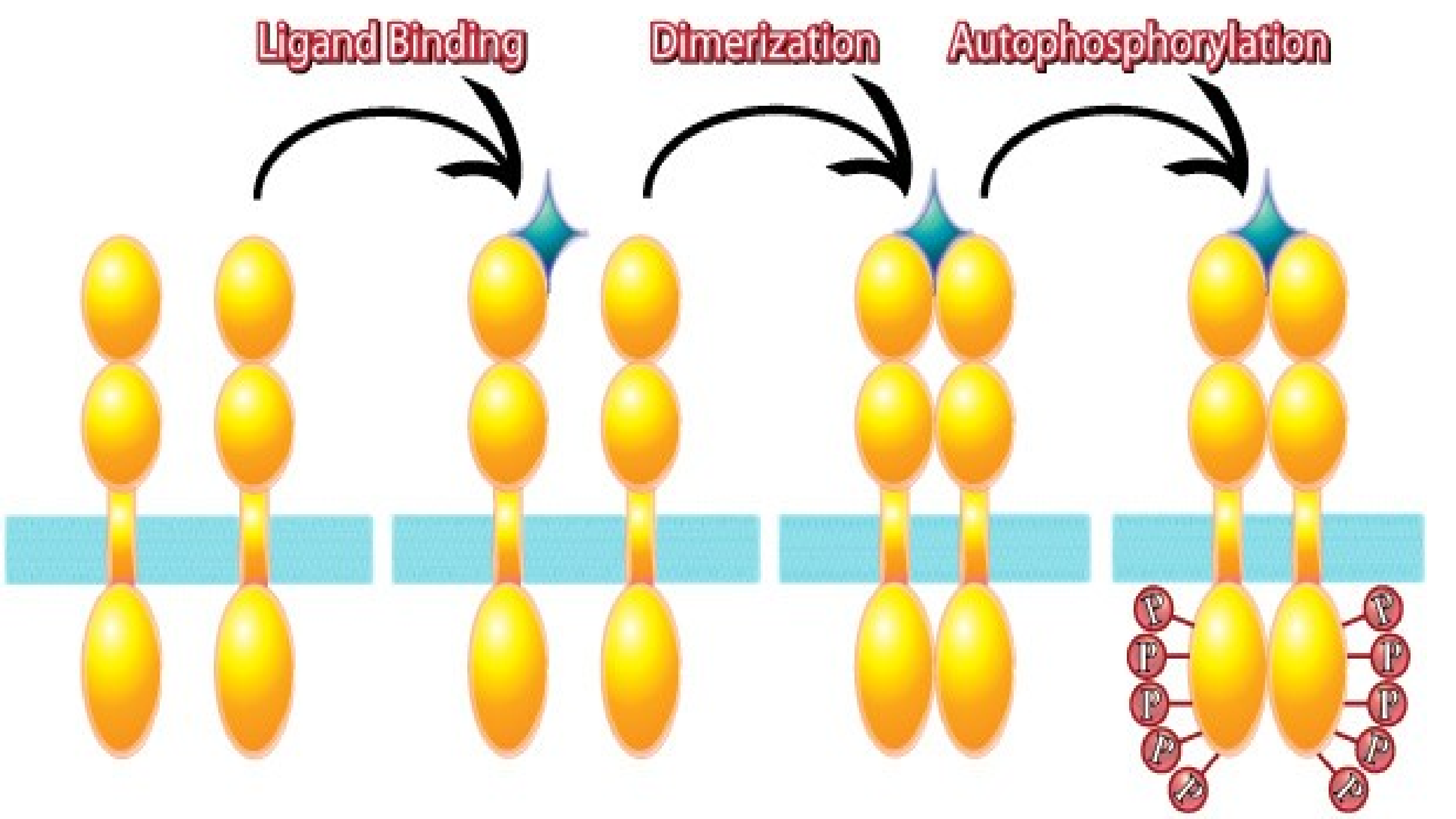
Tyrosine kinase receptors generally exist in the membrane as monomers

1- Growth factor binds two molecules of the receptor

2- Dimerization

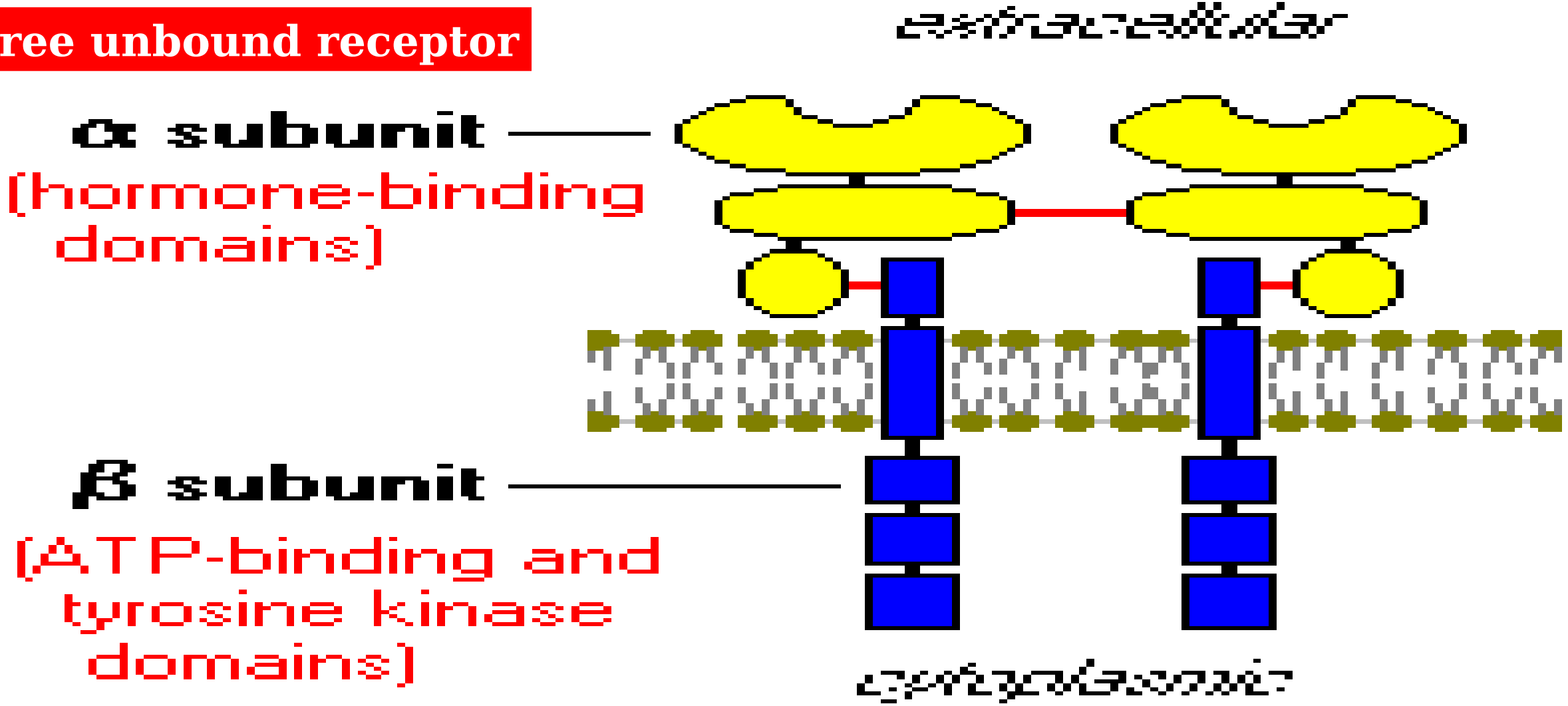
3- Autophosphorylation

4- Creation of specific binding sites for signal transducer proteins

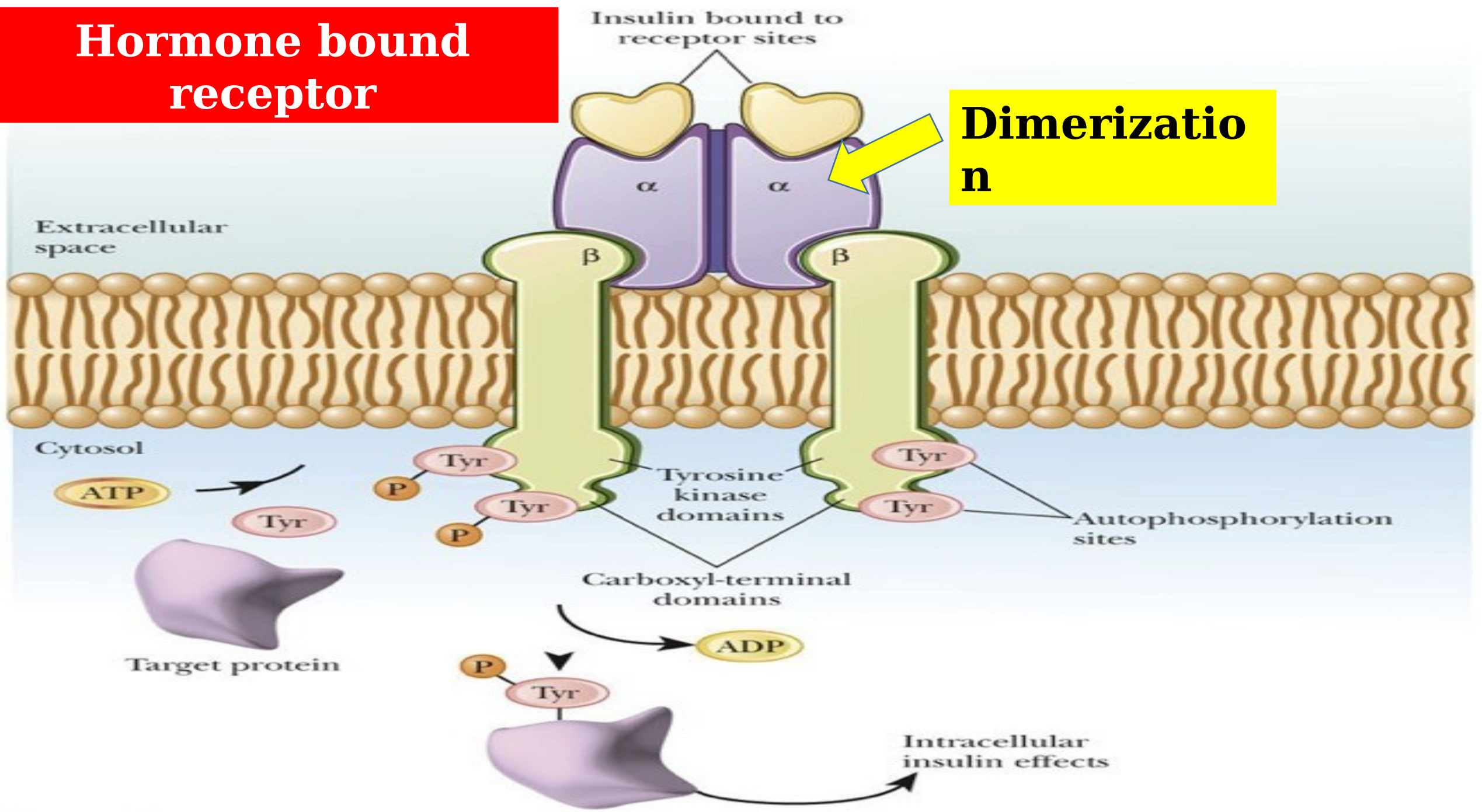

Ligand Binding
Dimerization
Autophosphorylation
P

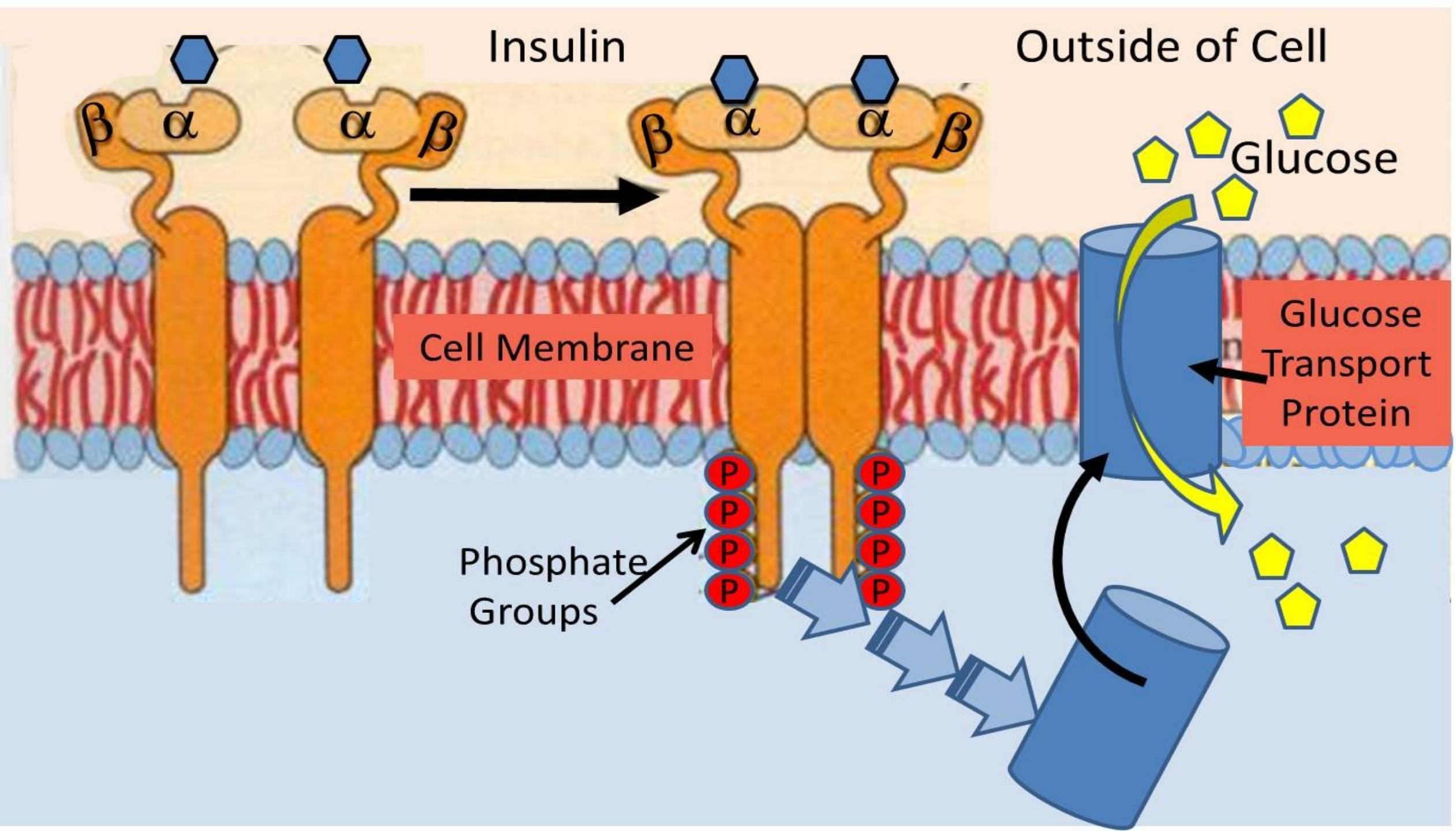
The insulin receptor

Free unbound receptor



Hormone bound receptor




Insulin
Outside of Cell
β
α
α
β
β
α
α
β
Glucose
Cell Membrane
Glucose
Transport
Protein
P
P
P
P
P
P
P
P
Phosphate
Groups

The insulin receptor

- The insulin receptor is a member of the tyrosine kinase family of receptors. It exists in the membrane as a dimer, consisting of two identical α subunits protruding from the outer face of the plasma membrane and two transmembrane β-subunits protruding into the cytosol.
- The α-subunits contain the insulin binding domain, and the intracellular domains of the β-subunits contain the tyrosine kinase activity.
- Signaling begins when insulin binding activates receptor *tyrosine kinase* activity in the intracellular domain of the β subunit.
- Tyrosine residues of the β subunit are autophosphorylated. This

The insulin receptor

- Receptor tyrosine kinase phosphorylates other proteins, for example, insulin receptor substrates (IRS).
- Phosphorylated IRS promotes activation of other protein kinases and phosphatases, leading to biologic actions of insulin.
- In this way, the receptor activates several enzyme cascades which produce the metabolic effects of insulin.
- Rapid effects as dephosphorylation of enzymes and increasing number of GLUT-4 in the membrane of muscle and adipose tissue and Delayed effects controlling gene expression.

Insulin binds to an insulin receptor of an adipocyte. Which of the following is a signaling process that will occur in response?

A. Activation of protein kinase C to phosphorylate substrates

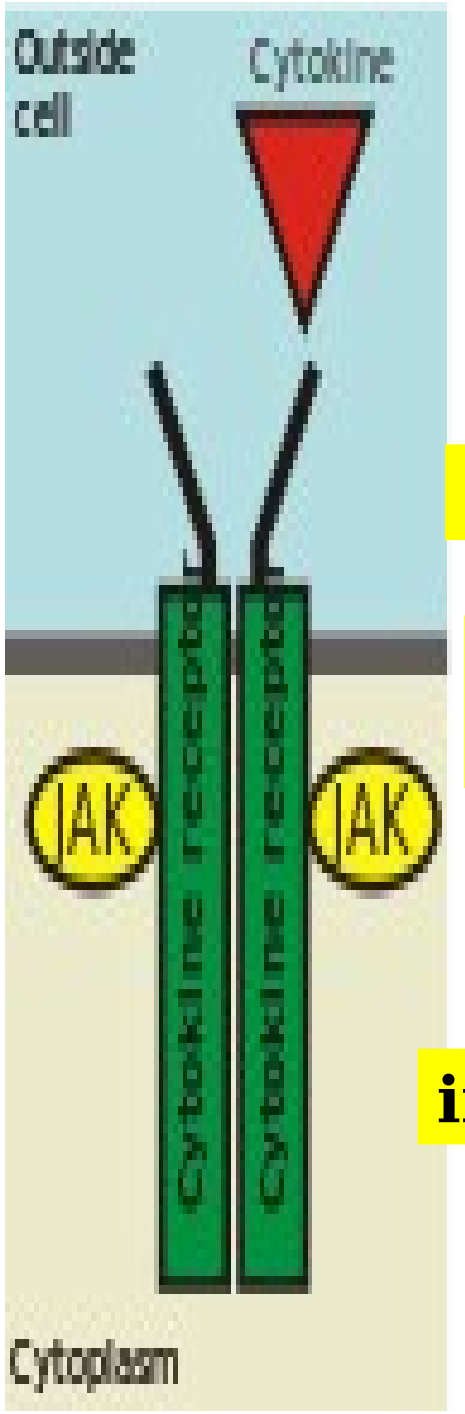
B. Adenylyl cyclase stimulation of cAMP production

C. G protein activation of second messenger production

D. Translocation of the insulin receptor to the cell's nucleus

E. Tyr phosphorylation of IRS

B- Signal transduction through receptors with no intrinsic tyrosine kinase activity but use cytoplasmic tyrosine kinase activity (JAK-STAT receptors):



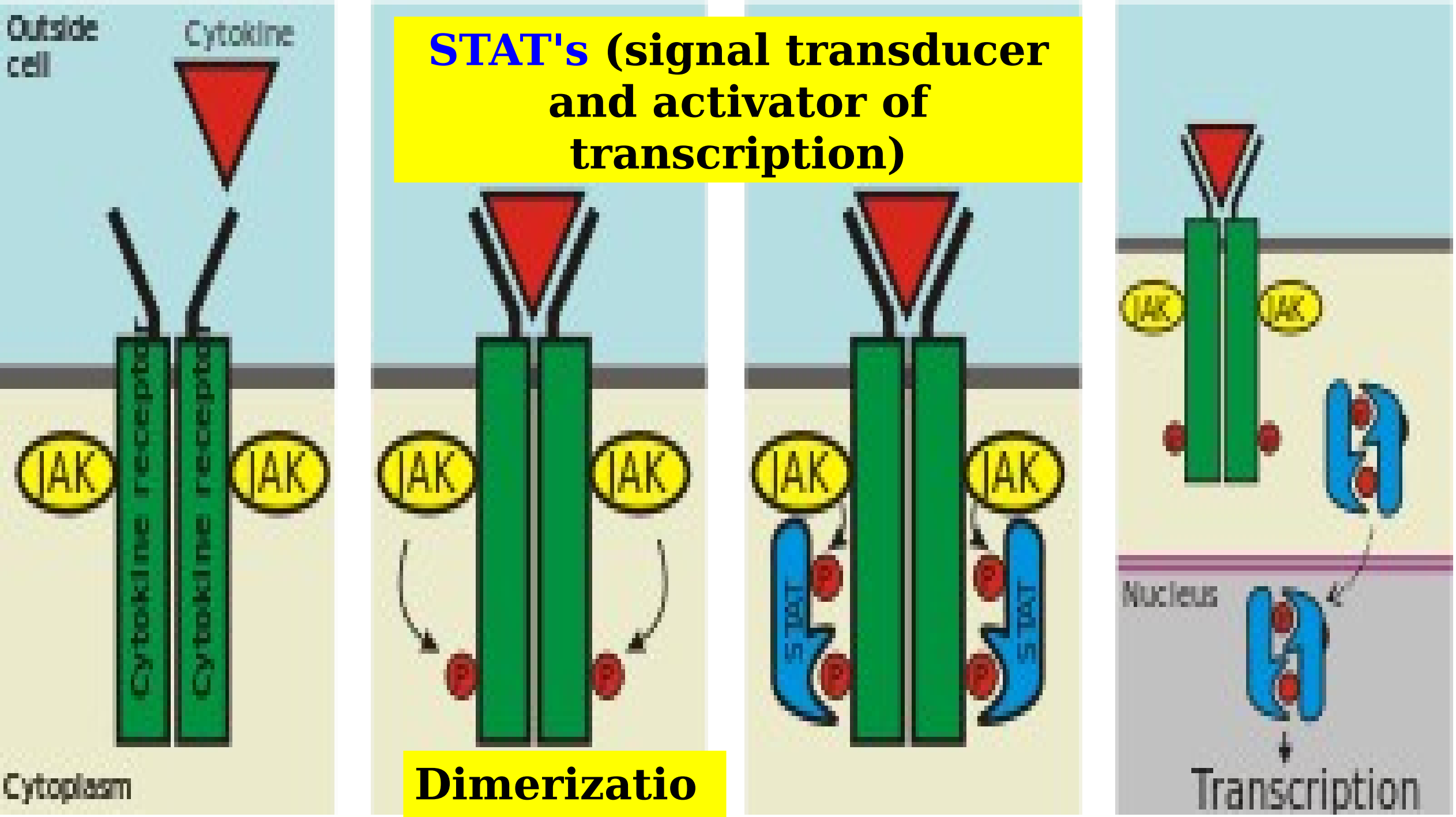
extracellular domain

membrane-spanning region

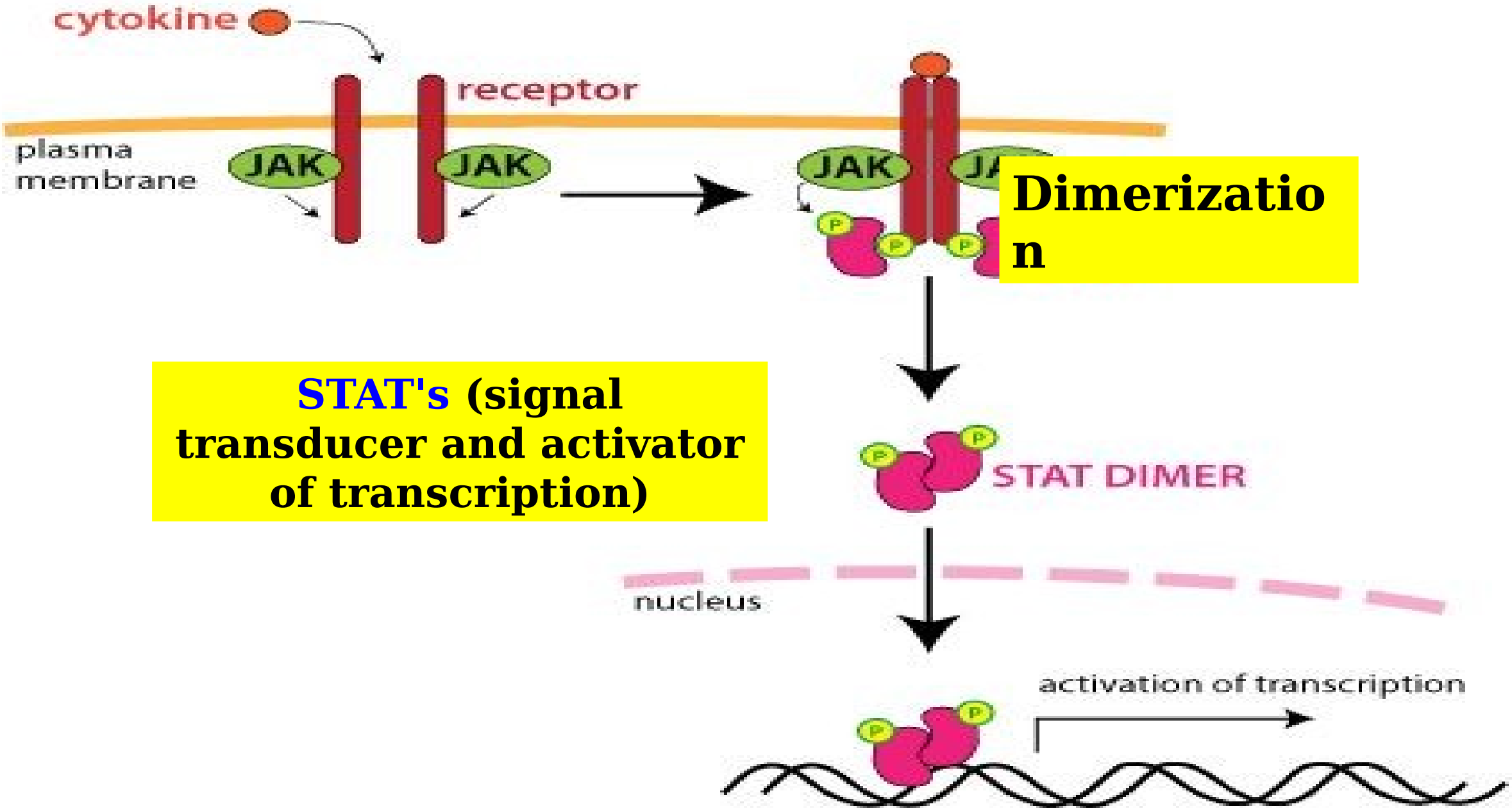
JAK
soluble tyrosine kinase

intracellular domain

STAT's (signal transducer and activator of transcription)



Dimerizatio



Dimerization

STAT's (signal transducer and activator of transcription)

1. **The cytokine binds the receptors**
2. **They dimerize**
3. **The receptor is activated and bind JAK**
4. **Active JAKs phosphorylate each other**
5. **Phosphorylate tyrosine residues on the receptor**
6. **STATs are phosphorylated by the bound JAK**
7. **The STAT dimer translocates to the nucleus and binds to a (HRE) on DNA**
8. **Regulate gene transcription**

Pathway	G Protein	Enzyme	Second Messenger(s)	Protein Kinase	Examples
cAMP	G_s (G_i)	Adenyl cyclase	cAMP	Protein kinase A	Glucagon Epinephrine (β, α-2) Vasopressin (V2, ADH) kidney
PIP_2	G_q	Phospholipase C	DAG, IP_3, Ca^{2+}	Protein kinase C	Vasopressin (V1, V3) vascular smooth muscle Epinephrine (α_1)
cGMP	None	Guanyl cyclase	cGMP	Protein kinase G	Atrial natriuretic factor (ANF) Nitric oxide (NO)
Insulin, growth factors	Monomeric $p21^{ras}$	—	—	Tyrosine kinase activity of receptor	Insulin Insulin-like growth factor (IGF) Platelet-derived growth factor (PDGF) Epidermal growth factor (EGF)

STATs function in signal transduction by:

A. Activating GTP binding to α subunits of G proteins.

B. Binding receptors phosphorylated on serine/ threonine residues.

C. Linking to G protein–coupled transmembrane receptors.

D. Phosphorylating substrates on Tyr residues.

E. Stimulating transcription of responsive genes.

Thank you